VIA EFS
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS :	Harrington	CONFIRMATION NO.:	5034
SERIAL NUMBER :	10/695,680	EXAMINER :	U. Ramachandran
FILING DATE :	October 29, 2003	ART UNIT :	1617
FOR :	COMPOSITIONS AND METHODS FOR PAIN REDUCTION		

DECLARATION OF J. FREDERICK HARRINGTON, JR. UNDER 37 C.F.R §1.132

I, J. Frederick Harrington, Jr., of Providence, Rhode Island, declare and state as follows:

1. I am the inventor of the invention claimed in the above-referenced application.

2. I received a M.D. degree from the Tufts University School of Medicine in 1983 and have been practicing in the field of Neurosurgery for 26 years. I have served as an Assistant Professor of Neurosurgery at Brown University School of Medicine and at University of Connecticut Health Center for 11 years. I have published over 60 peer-reviewed papers and abstracts in the field of Neurosurgery.

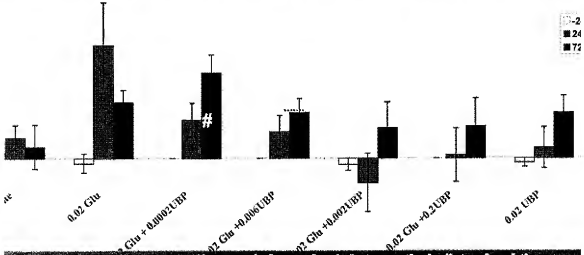
3. I have read the Office Action mailed on August 4, 2009 and am familiar with the Examiner's grounds of rejection of the pending claims. The data described in this declaration confirm the teachings of the originally-filed specification and demonstrate the reliability and predictability of the amended claims.

4. Glutamate receptor antagonists (KA receptor antagonist, a NMDA receptor antagonist, or an AMPA receptor antagonist) were tested in an established rat animal model. Adult breeder female rats were implanted with a miniosmotic pump in the epidural space that deposits 72 microliters of saline over 72 hours in the epidural space at the L5 level of the rat spine. To the saline .02 millimolar glutamate and varying

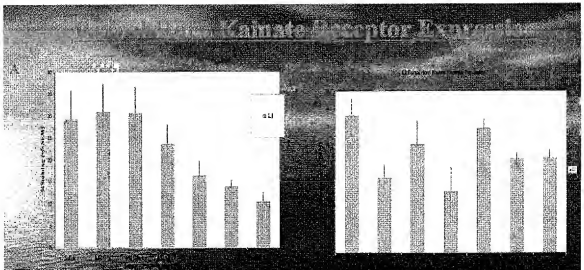
concentrations of an ionotropic glutamate receptor antagonist were added. Animals were assessed for relative hyperalgesia in the lower extremity by von Frey fiber testing 24 hours before and 24 and 72 hours after insertion of the pump. Animals were sacrificed and spinal cords were assessed for glutmate receptor expression changes in the L1 dorsal horn of the spinal cord, a parameter associated with nociceptive stimuli.

5. As demonstrated in the figure below, the specific kainic acid antagonist UBP-301 demonstrated dose dependant reversal of lower extremity hyperalgesia induced by the presence of 0.02mM glutamate concentration at both 24 and 72 hours after coinfusion with glutamate. Animals with increased glutamate alone in the epidural space demonstrated signs of pain.

[illegible] procedure hypersensitivity with an infusion of UBP-301



Von Frey fiber testing: differences in hyperalgesia between the ipsilateral and the contralateral hind limbs in response to a 72 hour glutamate/UBP301 infusion. Significant differences were seen in: 1)0.02mM Glutamate (*)p<0.01 @ -24hr vs. 24 hr and 72 hr); 2) 0.02mM Glu + 0.0002mM UBP (#)p<0.01 @ -24hr vs. 72hr) (Kruskal-Wallis test). With increaing UBP concentration beyond .0002MmM, glutamate based hyperalgesia is not present.



Changes in kainate receptor expression within the thoracolumbar dorsal horn (L1) in response to a 72 hour).02mmol/L glutamate infusion. Data are presented as mean % ± SEM. Statistical comparisons were made with 0.02mmol/L glutamate infused and glutamate plus UBP. Note progressive loss of expression with increasing BP-301 concentration at L1. *(N=5-9 rats per group).*

A:* Significant decreases were seen with 0.02 or 0.2mmol/L UBP or 0.02mmol/L UBP alone in L1. **p<0.02, **,#P<0.05,¶P<0.01. (Non parametric Kruskal-Wallis)

***B:* No significant differences at L2 (caudal to sensory nerve root insertion site)**

The specific NMDA receptor antagonist also reversed epidural based lower extremity hyperalgesia by both von Frey fiber testing and by immunohistochmical analysis of NMDA receptor activity in the dorsal horn.

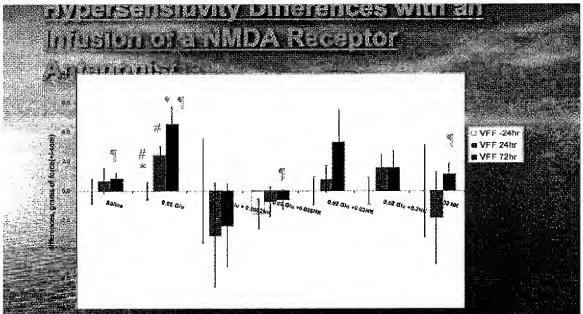


Fig 5. Von Frey Fiber testing measuring the difference in hyperalgesia between the contralateral and the ipsilateral hindlimbs in response to a 72 hour glutamate/Norketamine infusion at the L5 dorsal root ganglion. Lowest coinfusion concentration of norketamine obliterated glutamate induced hyperalgesia as did higher concentrations*(n=5-8 per group) ; *, ¶ p<0.05, (#)p<0.01 Kruskal-Wallis(Nonparametric ANOVA);*

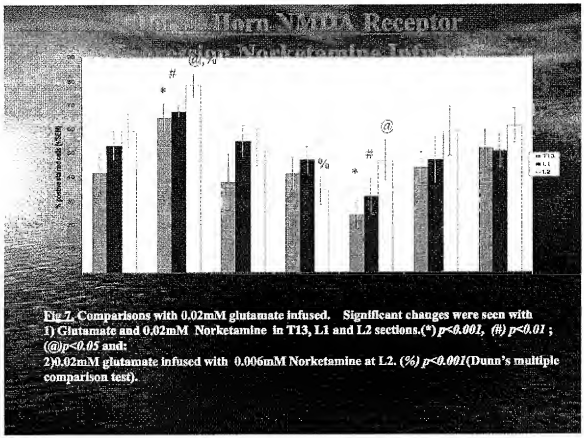
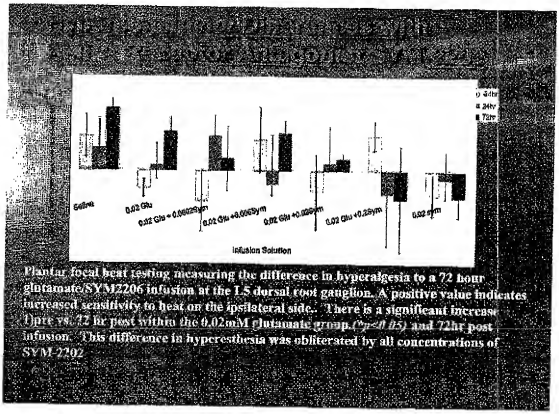


Fig 7. Comparisons with 0.02mM glutamate infused. Significant changes were seen with 1) Glutamate and 0.02mM Norketamine in T13, L1 and L2 sections.(*) *p<0.001*, (#) *p<0.01* ; (@)*p<0.05* and: 2)0.02mM glutamate infused with 0.006mM Norketamine at L2. (%) *p<0.001*(Dunn's multiple comparison test).

The specific AMPA receptor antagonist SYM-2202 demonstrated reversal of glutamate based hyperalgesia based on von Frey fiber testing.



Plantar focal heat testing measuring the difference in hyperalgesia to a 72 hour glutamate/SYM2206 infusion at the L5 dorsal root ganglion. A positive value indicates increased sensitivity to heat on the ipsilateral side. There is a significant increase (1pre vs. 72 hr post within the 0.02mM glutamate group, $^{*}p<0.05$) and 72hr post infusion. This difference in hyperesthesia was obliterated by all concentrations of SYM-2202

6. These results confirm the data described in the specification of the above-referenced patent application and demonstrate predictability of the claimed methods.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by a fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/4/09

J. Frederick Harrington, M.D.

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